

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 18002-10PC	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 99/ 12336	International filing date (day/month/year) 03/06/1999	(Earliest) Priority Date (day/month/year) 04/06/1998
Applicant REPROGEN, INC. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

contained in the international application in written form.

filed together with the international application in computer readable form.

furnished subsequently to this Authority in written form.

furnished subsequently to this Authority in computer readable form.

the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. **Certain claims were found unsearchable** (See Box I).

3. **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

the text is approved as submitted by the applicant.

the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

the text is approved as submitted by the applicant.

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

as suggested by the applicant.

because the applicant failed to suggest a figure.

because this figure better characterizes the invention.

—
 None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/12336

Box 1 Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims: it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim(s) 36-41 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition. Although claims 42, 43, 46-56 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/12336

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 C12Q1/68 G01N33/53

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHEDMinimum documentation searched (classification system followed by classification symbols)
 IPC 6 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	OTA AND IGARASHI: "EXPRESSION OF MAJOR HISTOCOMPATIBILITY COMPLEX CLASS II ANTIGEN IN ENDOMETRIC TISSUE IN PATIENTS WITH ENDOMETRIOSIS AND ADENOMYOSIS" FERTIL STERIL, vol. 60, no. 5, 1993, pages 834-838, XP000857027 the whole document ---	1-56
Y	BAXEVANIS ET AL.: "PROTHYMOIN ALPHA ENHANCES HUMAN AND MURINE MHC CLASS II SURFACE ANTIGEN EXPRESSION AND MESSENGER RNA ACCUMULATION" J. IMMUNOL., vol. 148, no. 7, 1992, pages 1979-1984, XP002125674 the whole document --- ---	1-56

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

15 December 1999

29/12/1999

Name and mailing address of the ISA
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Hagenmaier, S

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/12336

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 32708 A (LYNXVALE LTD ;CHARNOCK JONES DAVID STEPHEN (GB); MCLAREN JOHN (GB)) 7 December 1995 (1995-12-07) the whole document ---	1-56
Y	HILL: "IMMUNOLOGY AND ENDOMETRIOSIS" OBSTET GYNECOL CLIN NORTH AM, vol. 24, no. 2, 1997, pages 291-306, XP000857031 the whole document ---	1-56
A	SHARPE-TIMMS: "BASIC RESEARCH IN ENDOMETRIOSIS" OBSTETRICS AND GYNECOLOGY CLINICS OF NORTH AMERICA, vol. 24, no. 2, June 1997 (1997-06), pages 269-290, XP000853792 the whole document ---	
A	US 5 248 591 A (PUENTE FERNANDO D) 28 September 1993 (1993-09-28) the whole document ---	
A	WO 98 12324 A (BLOOD RES CENTER) 26 March 1998 (1998-03-26) See page 4, line 28 the whole document ---	
A	US 4 696 915 A (HORECKER BERNARD L) 29 September 1987 (1987-09-29) the whole document ---	
A	OIKAWA ET AL.: "EXPRESSION OF GONADOTROPIN-RELEASING HORMONE AND PROTHYMOSEIN-ALPHA MESSENGER RIBONUCLEIC ACID IN THE OVARY" ENDOCRINOLOGY, vol. 127, no. 5, 1990, XP000857700 the whole document ---	
P, Y	DATABASE MEDLINE 'Online! HUMAN REPROD UPDATE, July 1998 (1998-07) OTA ET AL.: "IS ADENOMYOSIS AN IMMUNE DISEASE" XP002123261 abstract ---	1-56
P, Y	WO 98 42185 A (DEERLIN PETER VAN ;UNIV PENNSYLVANIA (US); BOYD JEFFREY (US); REPR) 1 October 1998 (1998-10-01) the whole document -----	1-56

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/12336

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9532708	A 07-12-1995	AU 692874	B	18-06-1998
		AU 2535395	A	21-12-1995
		CA 2191070	A	07-12-1995
		EP 0771192	A	07-05-1997
		JP 10505321	T	26-05-1998
		NZ 285833	A	29-09-1999
US 5248591	A 28-09-1993	NONE		
WO 9812324	A 26-03-1998	AU 4342197	A	14-04-1998
		EP 0960202	A	01-12-1999
US 4696915	A 29-09-1987	NONE		
WO 9842185	A 01-10-1998	AU 6584798	A	20-10-1998

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Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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Generaldirektion 2

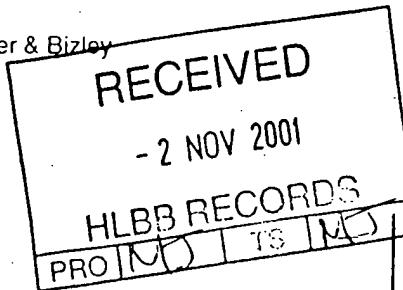
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(Formalities and other matters)



Application No. 99 926 150.6-1222	Ref. APEP 00514	Date 31.10.2001
Applicant Reprogen, Inc.		

Communication pursuant to Article 96(2) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(1) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 78(2) and 83(2) and (4) EPC.

Amendments to the description, claims and drawings are to be filed where appropriate within the said period in three copies on separate sheets (Rule 36(1) EPC).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Article 96(3) EPC).



AGUILERA MERLO M
Primary Examiner
for the Examining Division

Enclosure(s): 7 page/s reasons (Form 2906)



Beschluß/Protokoll (Anlage)	Communication/Minutes (Annex)	Notification/Procès-verbal (Annexe)
Datum Date Date 31.10.2001	Blatt Sheet Feuille 1	Anmelde-Nr.: Application No.: Demande n°: 99 926 150.6

The examination is being carried out on the following application documents:

Text for the Contracting States:

AT BE CH LI CY DÉ DK ES FI FR GB GR IE IT LU MC NL PT SE

Description, pages:

1-48 as published

Claims, No.:

1-30 as received on 28.02.2000 with letter of 28.02.2000

1 AMENDMENTS (Article 123(2) EPC)

- 1.1 The incorporation of the subject-matter of some dependent claims from the set filed on 03.06.1998 (original set) into claims filed on 02.03.2000 (new set) as optional features gives rise to a high number of new specific combinations of features that do not appear to be disclosed as such in the original document.
 - 1.1.1 For example, independent claim 1 in the new set incorporates the subject-matter of claims 3, 14 and 22 of the original set. In the same manner, claim 3 in the new set incorporates the subject-matter of claims 3, 5 and 15 of the original set. Therefore, all claims in the new set dependent on claim 1 or on claim 3, directly or indirectly, include new specific combinations of features.
 - 1.1.2 Further examples are found in claims 5-8 of the new set. The dependency of these claims does not seem to correspond to the dependency of equivalent claims in the original set, giving rise to specific new combinations of features.
- 1.2 Therefore, at least some of the amendments seem not to be supported in the application as filed, and are not allowable under Article 123(2) EPC. If the applicant can however prove the contrary, he is requested to indicate the passages of the application as filed on which these amendments are based, specially for the new combinations of features generated by the new claim structure. It would be appropriate to submit these indications in handwritten form on a copy of the relevant parts of the application as filed.



Bescheld/Protokoll (Anlage)	Communication/Minutes (Annex)	Notification/Procès-verbal (Annexe)
Datum Date Date	31.10.2001	Blatt Sheet Feuille

1.3 In order to accelerate the granting process, the new set of claims (02.03.200) was used as the basis for examination. However, the conclusions reached in this communication can only be maintained if the Applicant can prove that the requirements of Article 123(2) are met.

2 CITED DOCUMENTS

2.1 The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: OIKAWA ET AL.: 'EXPRESSION OF GONADOTROPIN-RELEASING HORMONE AND PROTHYMOSEN-ALPHA MESSENGER RIBONUCLEIC ACID IN THE OVARY' ENDOCRINOLOGY, vol. 127, no. 5 (1990)

D2: US-A-5 248 591 (PUENTE FERNANDO D) 28 September 1993

2.2 The following documents (D) are cited by the examiner (see the Guidelines, C-VI, 8.9). Copies of the documents are annexed to the communication and the numbering will be adhered to in the rest of the procedure:

D3: GIUDICE ET AL.: "STATUS OF CURRENT RESEARCH ON ENDOMETRIOSIS" J REPROD MED, vol. 43, pages 252-262 (March 1998)

D4: SBURLATI ET AL: "PROTHYMOSEN ALPHA ANTISENSE OLIGOMERS INHIBIT MYELOMA CELL DIVISION", PROC. NAT. ACAD. SCI. USA, vol. 88, no. 1, pages 253 to 257 (January 1991).

D5: MEDLINE (Abstract, PMID 9185507): BRUNER ET AL: "SUPPRESSION OF MATRIX METALLOPROTEINASES INHIBITS ESTABLISHMENT OF ECTOPIC LESIONS BY HUMAN ENDOMETRIUM IN NUDE MICE", J. CLIN. INVEST. vol. 99, no. 12, pages 2851-2857 (15 June 1997)



Beschied/Protokoll (Anlage)	Communication/Minutes (Annex)	Notification/Procès-verbal (Annexe)
Datum Date Date: 31.10.2001	Blatt Sheet Feuille: 3	Anmelde-Nr.: Application No.: 99 926 150.6 Demande n°:

3 EXCLUSIONS FROM PATENTABILITY (Article 52 EPC)

3.1 The methods of claims 17-21 are to be practised *in vivo* on the human or animal body, and therefore not susceptible of industrial application. These methods are not patentable inventions according to Article 52(4) EPC.

4 NOVELTY (Art. 54 EPC)

4.1 The subject-matter of claims 15, 16 and 30 is not new in view of D1, describing a radioactively labelled cRNA probe that specifically binds a 462 bp segment of prothymosin alpha RNA (cf. page 2352, column 1). The "instructions" to use a prothymosin probe in the diagnosis of endometriosis are not components of a technical character, and therefore, they are not considered as a technical feature of the product with regard to Article 54 EPC.

5 INVENTIVE STEP (Art. 56 EPC)

5.1 Claim 1:

5.1.1 Document D3 is considered to represent the most relevant state of the art. It discloses that, although endometriosis is not a malignant disorder, it exhibits features characteristic of proliferative diseases, like cellular proliferation, cellular invasion and neoangiogenesis (cf. Abstract). The ectopic endometrial tissue must proliferate and establish a blood supply in order to implant and develop (cf. page 252, column 2, lines 19-22). D3 also discloses that the peritoneal fluid from women with endometriosis has mitogenic activities (cf. page 257, column 2, lines 38-40) due to its increased content in EGF, IGF, PDGF and other growth factors with shown effects in the proliferation of endometrial cells (cf. page 258, column 1, line 16, to page 259, column 1, line 5; Table III). The teaching of D3 on the etiology of endometriosis confirms the need for new reliable diagnostic methods.

5.1.2 The subject-matter of claim 1 differs from prior art in the use of prothymosin overexpression as a diagnostic marker for endometriosis.



Beschluß/Protokoll (Anlage)	Communication/Minutes (Annex)	Notification/Procès-verbal (Annexe)
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5.1.3 The problem to be solved by the present invention may therefore be regarded as providing a method for the diagnosis of endometriosis. The proposed solution is to use prothymosin as a marker in the analysis of endometriotic samples, based on the fact that endometriotic tissue overexpresses prothymosin.

5.1.4 This solution cannot however be considered as involving an inventive step in view of D2, which discloses a method of diagnosis of cancer and other proliferative disorders based on the expression levels of prothymosin alpha (cf. column 1, lines 51-55). The implication of prothymosin alpha in cell proliferation is well known in the field, and document D2 describes that prothymosin alpha levels in tumor samples from breast cancer are higher than the levels found in adjacent normal breast tissue samples (cf. column 2, lines 33-35). A method of estimating the risk of recurrence or metastasis of breast cancer is also claimed in D2. This method comprises the steps of measuring the prothymosin alpha levels in a tumor sample, and comparing the measured amount with a control sample, wherein a high amount of prothymosin indicates a high risk of recurrence or metastasis (cf. claim 1).

5.1.5 In view of the above, the skilled person would be prompted to use prothymosin as a marker in the analysis of endometriotic samples with a high expectation of success. Therefore, the method of claim 1 does not involve an inventive step in the sense of Article 56 EPC.

5.1.6 Dependent claims 2-13 do not appear to contain any additional features which, in combination with the features of any claim to which they refer, involve an inventive step because they describe standard laboratory methods of detecting the product of a gene, be it mRNA or protein. A person skilled in the art would regard it a normal experimental design procedure to choose or combine the known techniques and tools at the time of the invention in order to solve the problem posed.

5.2 The method of claim 14 is essentially the same as the method of claim 1, the difference being the sample to be used as a control, normal endometrial tissue, or the endometrial tissue of the same patient in an earlier time. However, the



Bescheid/Protokoll (Anlage)		Communication/Minutes (Annex)		Notification/Procès-verbal (Annexe)	
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skilled person would regard as a normal option to compare the prothymosin amounts of the same subject at two different times, instead of comparing it to a control sample, in order to obtain a diagnostic indication of the progression of endometriosis in this subject. Therefore, the subject-matter of claim 14 is not inventive in the sense of Article 56 EPC.

5.3 Claim 22:

- 5.3.1 D4 is considered to represent the most relevant state of the art, and discloses the use of four different compounds (antisense oligonucleotides) for the inhibition of prothymosin alpha expression in myeloma cells (cf. page 253, column 1, paragraph 3; page 256, paragraph 2). Though with a different purpose, this study can implicitly be considered as a screening for compounds blocking the activity of prothymosin.
- 5.3.2 The subject-matter of claim 22 differs in that the cells to be used are endometrial cells instead of myeloma cells.
- 5.3.3 The problem to be solved by the present invention may be regarded therefore as providing an alternative cell system for screening.
- 5.3.4 The proposed solution cannot however be considered as involving an inventive step over D4 because the skilled person would regard it a normal experimental design option to use any kind of endometrial cells instead of myeloma cells in order to solve the problem posed.
- 5.3.5 Dependent claim 23 does not contain any additional features which, in combination with the features of claim 22, involve an inventive step, because the use of nude mice as recipients for human endometriotic tissue in the study of endometriosis has been previously disclosed (cf. D5, Abstract), and a person skilled in the art would regard it as an experimental design option.

- 5.4 The subject-matter of claims 24-29 is not considered to involve an inventive step over prior art. The relation between prothymosin overexpression and endometriosis as a proliferative disease is not considered inventive (see above),



Beschied/Protokoll (Anlage)	Communication/Minutes (Annex)	Notification/Procès-verbal (Annexe)
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and therefore, the use of a compound decreasing the activity of prothymosin as a therapeutic agent is considered obvious.

5.5 In view of the above, the present application does not meet the requirements of Article 52(1) EPC, because the subject-matter of claims 1-16 and 22-30 does not involve an inventive step in the sense of Article 56 EPC.

6 CLARITY (Art. 84 EPC)

6.1 Claims 24-29 are not supported by the description as required by Article 84 EPC. Their scope is broader than justified by the description and drawings because no evidence of the use of compounds decreasing the activity of prothymosin in the treatment of endometriosis is shown in the description.

6.2 The term "prothymosin" in claims 1-30 and description is not common use in the field. The name used in the literature and sequence databases is "prothymosin alpha". If they refer to the same gene, the applicant is invited to provide evidence in support of this fact. If they do not, claims should include a reference to the definition of "prothymosin" in terms of SEQ ID NO:1 and/or 2, at least in the first independent claim.

7 CONCLUSIONS

7.1 The applicant is invited to provide his arguments. Although it is not at present apparent which part of the application could serve as a basis for a new, allowable claim, if the applicant regards some particular matter as patentable, an independent claim including such matter should be filed taking account of Rule 29(1) EPC. The applicant should also indicate in the letter of reply the difference of the subject-matter of the new claim vis-à-vis the state of the art and the significance thereof.

7.2 If filing amended claims the applicant should at the same time bring the description into conformity with the amended claims. Care should be taken during revision,



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especially of the introductory portion and any statements of problem or advantage, not to add subject-matter which extends beyond the content of the application as originally filed (Article 123(2) EPC).

- 7.3 In order to facilitate the examination of the conformity of the amended application with the requirements of Article 123(2) EPC, the applicant is requested to clearly identify the amendments carried out, and to indicate the passages of the application as filed on which these amendments are based. If the applicant regards it as appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.
- 7.4 To meet the requirements of Rule 27(1)(b) EPC, documents D1-D5 should be identified in the description and the relevant background art disclosed therein should be briefly discussed.

Miguel Aguilera Merlo



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C12Q 1/68, G01N 33/53		A2	(11) International Publication Number: WO 99/63116 (43) International Publication Date: 9 December 1999 (09.12.99)
(21) International Application Number: PCT/US99/12336			(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 3 June 1999 (03.06.99)			
(30) Priority Data: 60/088,016 4 June 1998 (04.06.98)	US		
(71) Applicant (for all designated States except US): REPROGEN, INC. [US/US]; Suite 210, 163 Technology Drive, Irvine, CA 92618 (US).			
(72) Inventors; and			
(75) Inventors/Applicants (for US only): <u>SCHNEIDER</u> , Patrick, A. [US/US]; 49 Castillo, Irvine, CA 92620 (US). <u>FRENCH</u> , Cynthia, K. [US/US]; 14 Virgil Court, Irvine, CA 92612 (US). <u>YAMAMOTO</u> , Karen, K. [US/US]; 524 West Avenida de los Lobos Marinos, San Clemente, CA 92672 (US).			
(74) Agents: STORELLA, John, R. et al.; Townsend and Townsend and Crew LLP, 8th floor, Two Embarcadero Center, San Francisco, CA 94111-3834 (US).			

(54) Title: USE OF PROTHYMOSEN IN THE DIAGNOSIS AND TREATMENT OF ENDOMETRIOSIS

(57) Abstract

Prothymosin expression is up-regulated in endometriotic tissue. This invention provides methods of diagnosing endometriosis by detecting up-regulation of a prothymosin gene product, and methods of treating endometriosis by down-regulating expression of prothymosin in ectopic or eutopic endometriotic tissue.

Published

Without international search report and to be republished upon receipt of that report.